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Research Article

APPROVAL OF NEW NERVOUS SYSTEM DRUGS IN INDIA COMPARED WITH THE US AND EU

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ABSTRACT

Objective: The drug lag in approval of nervous system drugs between India and developed countries has been a major issue both for patients and healthcare professionals. The objective of this study was to assess the drug lag for new nervous system drugs in India compared with that in the United States (US) or European Union (EU).

Materials and Methods: New nervous system drugs approved in the United States, European Union and India between 1999 and 2011 were identified and information was gathered primarily from the websites of regulatory agencies of the three regions. We assessed absolute and relative drug lag for new nervous system drugs approved in the three regions.

Results: Of the 97 new nervous system drugs, 72 (74.22%) were approved in the United States, 76 (78.35%) in the European Union and 75 (77.31%) in India. The US was the first to approve 32 (41.03%) out of the 97 new nervous system drugs, the EU was the first to approve 39 (50%) and India was the first to approve 7 (8.97%). The median approval lag for India (48.95 months) was substantially higher as compared to the United States (0 month) and European Union (0 month).

Conclusion: This study confirms that there is a large gap between India and the United States or European Union with regard to access to new nervous system drugs. The impact of the drug lag on health outcomes remains to be established.

Keywords: Neurology, Psychiatric drug, Marketing approval, Drug lag, New drug development, Regulatory authority

INTRODUCTION

The last two decades has seen remarkable advances in the therapeutic abilities of the neurologists and psychiatrists. The spectrum of neurological disorders or psychiatry problems seen in India is similar to that of other parts of the world.[1] However; Indian patients are not getting access to the new medicines at the same time as patients in the developed nations. The timeliness with which drug regulatory authorities approve new drugs for marketing affects health care professionals and patients. A long approval process delays access to new medicines that may improve patients' health status. Drug lag has been a debated issue in the United States (US) and Europe during the 1970s and 1980s.[2-3] However, the drug lag issue has not been addressed seriously in India. Because of increasing use of internet in India, many healthcare professionals and general public are now aware of the treatment options available in the developed regions.

Each country has specific regulatory controls that govern approval of new drugs; however, these controls often differ from country to country. Therefore, the time required for approval of a new drug may vary depending on each country's regulatory process. There is a change in the regulatory environment after a system of product patents in India since 2005.[4] The main regulatory body for the Indian pharmaceutical industry is the Central Drugs Standard Control Organization (CDSCO). The Drug Controller General of India (DCGI) is the controlling body for the CDSCO. The office of the Drug Controller General of India is responsible for the approval of new drugs and clinical trials.

The drug lag prevents Indian patients from accessing new drugs at the same time as patients in the developed nations. Further, it may even delay the progress of clinical research in India. Therefore, identifying the actual status of the nervous system drug lag in India would provide important information that could be used in efforts to resolve this issue. The purpose of this study was to assess the drug lag for new nervous system drugs approved in India, in comparison with the approval of new nervous system drugs in developed regions like the US and European Union (EU).

MATERIALS AND METHODS

Identification of new nervous system drugs

New drugs approved in the US, EU, or India between 1999 and 2011 were identified by searching the regulatory agencies online databases. The US data were obtained from the US Food and Drug Administration (FDA) website.[5] The EU data were obtained from the European Medicines Agency (EMA) website[6] and Indian data were obtained from the Central Drugs Standard Control Organization (CDSCO) website.[7] For the drugs identified, the WHO Anatomical Therapeutic Chemical (ATC) classification codes were assigned to determine the therapeutic group for each drug (e.g. ATC code for Duloxetine is N06AX21).[8] We analysed nervous system drugs from the fourteen main groups of the ATC classification system. Information about indication and date of issue of marketing approval was retrieved from the above sources. New drugs were defined as drugs having an active ingredient that has never before been marketed in the US, EU or India in any form. The following drugs were excluded: (a) vaccines and (b) combination drugs that do not include any new drugs.

Analyses of drug lag

In this study, we assessed and described the drug lag in the three regions in terms of 'absolute drug lag' and 'relative drug lag'. In assessing absolute drug lag, we used as variables the number and the percentage of approved new nervous system drugs in each region out of a total of new nervous system drugs approved either in the three regions in the study period. In assessing relative drug lag, two variables were used; one variable was the number and percentage of first approvals in the regions out of a total of new nervous system drugs approved either in the three regions in the study period, and the other variable was the approval lag against the first approval granted to each nervous system drug in the three regions. For example, if the US was the first to approve a nervous system drug in March 2009 and if India approved the same nervous system drug in December 2009, the approval lag for the US is 0, and the approval lag for India is 9 months.

The approval lag was obtained for all new nervous system drugs approved in each region, and the median approval lag was calculated for each region. In the European Union (EU), the European Medicines Agency (EMA) was established in 1993 to unify regulatory practice within the EU. The centralized procedure for marketing authorization of drugs throughout the EU went into operation in 1995. So alternatively we searched UK approval date for the nervous system drugs for which EU approval date was not available. The UK approval dates were obtained from the Electronic Medicines Compendium.[9] The new nervous system drugs for which approval

dates were unknown were excluded from the calculation of median approval lag.

Additionally, for the FDA approved drugs, the information about review type (standard/priority/orphan drug status) was obtained from the FDA online database.

RESULTS

New nervous system drugs approved in the US, EU and India

We identified 97 new nervous system drugs approved either in the US, the EU, or India between 1999 and 2011. Of these 97 new nervous system drugs, 38 were mutually approved in the three regions. The US and the EU approved 22 nervous system drugs that were not approved in India. The EU and India approved 25 nervous system drugs that were not approved in the US. The US and India approved 21 nervous system drugs that were not approved in the EU. Total 72 new nervous system drugs were approved in India during the period of 1999 to 2011, with an average of 5.53 new nervous system drugs approved per year. For the same period a total of 46 new nervous system drugs were approved in the US, with an average of 3.53 nervous system drugs approved per year and in the EU a total of 25 new nervous system drugs were approved, with an average of 1.92 nervous system drugs approved per year. The year wise distribution of new nervous system drugs approved in the US, EU and India is shown in Figure 1.

Analyses of drug lag

The absolute drug lags for the US, the EU and India are shown in Table 1. Of the 97 new nervous system drugs, 72 (74.22%) were approved in the US, 76 (78.35%) in the EU and 75 (77.31%) in India.

The relative drug lags for the US, the EU and India are summarized in Table 1. The US was the first to approve 32 (41.03%) out of the 97 new nervous system drugs, the EU was the first to approve 39 (50%) and India was the first to approve 7 (8.97%). The median approval lag for India (48.95 months) was substantially higher as compared to the United States (0 month) and European Union (0 month). The distributions of approval lags for each region are shown in Figure 2. Although the approval lag was less than one year for most of the nervous system drugs for the US and the EU, India had a different distribution profile. The 10 new nervous system drugs were approved in India within first 12 months of drug lag interval and showed a wide distribution up to nearly 201 months (Figure 2).

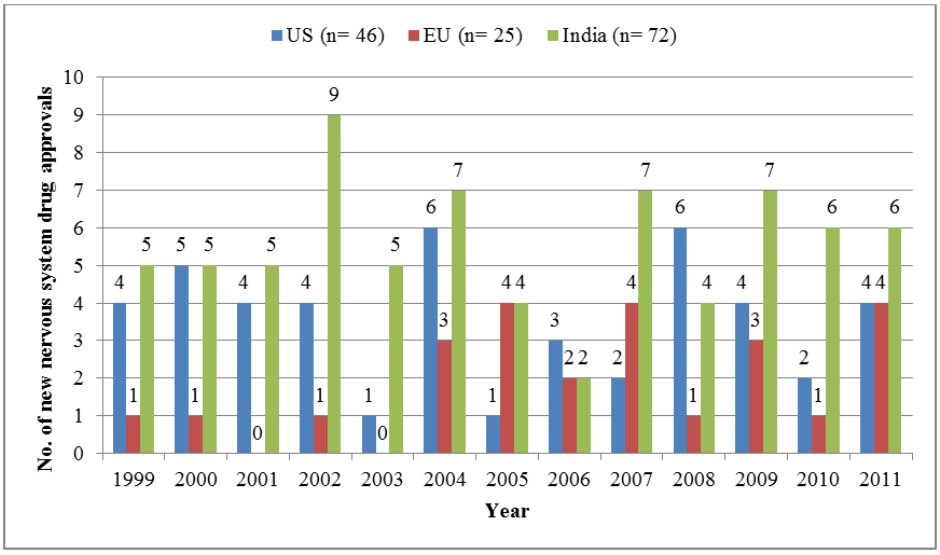

Fig. 1: New nervous system drugs approved in the US, EU and India, 1999-2011.

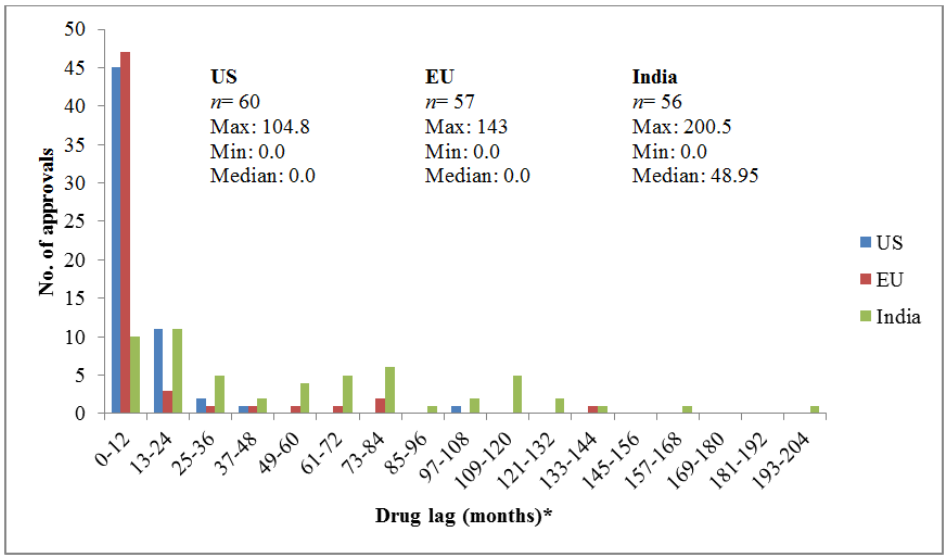

Fig. 2: Distribution of drug lag for new nervous system drugs approved in the US, EU and India

*The distribution is shown in 12-month interval

Table 1: Absolute and relative drug lag of new nervous system drugs for the US, the EU and India (*n*= 97)

	US	EU	India
Number of approvals	72 (74.22%)	76 (78.35%)	75 (77.31%)
Number of first approvals	32 (41.03%)	39 (50%)	7 (8.97%)
Median approval lag (months)	0 (*n*= 60)	0 (*n*= 57)	48.95 (*n*= 56)

The relative drug lag was assessed for the 38 'mutually approved new nervous system drugs'. The US was the first to approve 15 (39.47%) out of the 38 mutually approved new nervous system drugs, the EU was the first to approve 23 (60.53%) and India was the first to approve 0 (0.00%). Again the median approval lag for India (61.9 months) was substantially higher as compared to the United States (1.95 months) and European Union (0 month) for the mutually approved nervous system drugs.

Table 2: Approval dates and characteristics of new nervous system drugs approved either in the US, EU or India from 1999 through 2011 (*n*= 97)

Generic name (INN)	Indication	US approval date	EU approval date	India approval date	US review type
Vilazodone	Major depressive disorder	21-Jan-2011	NA	NA	S
Gabapentin enacarbil	Primary restless legs syndrome	6-Apr-2011	NA	NA	S
Ezogabine	Epilepsy	10-Jun-2011	NA	NA	S
Clobazam	Epilepsy	21-Oct-2011	A	A	S,O
Dalfampridine	Multiple sclerosis	22-Jan-2010	NA	NA	P,O
Lurasidone	Schizophrenia	28-Oct-2010	NA	NA	S
Milnacipran	Fibromyalgia syndrome	14-Jan-2009	NA	22-May-2008	S
Iloperidone	Schizophrenia	6-May-2009	NA	17-Feb-2011	S
Asenapine	Schizophrenia	13-Aug-2009	1-Sep-2010	7-Apr-2011	S
Vigabatrin	Epilepsy	21-Aug-2009	A	A	S,O
Desvenlafaxine	Major depressive disorder	29-Feb-2008	NA	18-Jul-2009	S
Tetrabenazine	Chorea of huntington's disease	15-Aug-2008	A	10-Mar-1999	P,O
Lacosamide	Epilepsy	28-Oct-2008	29-Aug-2008	10-Jun-2010	S
Rufinamide	Epilepsy	14-Nov-2008	16-Jan-2007	NA	S,O
Tapentadol*	Moderate to severe acute pain	20-Nov-2008	4-Feb-2011	18-Apr-2011	S
Fospropofol	Sedation	12-Dec-2008	NA	NA	S
Lisdexamfetamine	ADHD	23-Feb-2007	NA	NA	S
Rotigotine	Parkinson's disease	9-May-2007	15-Feb-2006	NA	S
Varenicline	Smoking cessation	10-May-2006	26-Sep-2006	29-May-2007	P
Rasagiline	Parkinson's disease	16-May-2006	21-Feb-2005	31-Jan-2009	S
Paliperidone	Schizophrenia	19-Dec-2006	25-Jun-2007	26-Sep-2008	S
Ramelteon	Insomnia	22-Jul-2005	NA	15-Dec-2010	S
Apomorphine	Parkinson's disease	20-Apr-2004	28-May-2001	12-Nov-2007	P,O
Acamprosate*	Abstinence from alcohol	29-Jul-2004	18-Dec-1995	30-Oct-2002	P
Duloxetine	Major depressive disorder	3-Aug-2004	11-Aug-2004	2-Nov-2004	S
Eszopiclone	Insomnia	15-Dec-2004	NA	7-Feb-2007	S
Ziconotide	Severe chronic pain	28-Dec-2004	21-Feb-2005	NA	P
Pregabalin	Neuropathic pain	30-Dec-2004	6-Jul-2004	25-Nov-2005	P
Memantine	Alzheimer's disease	16-Oct-2003	15-May-2002	19-Jul-2004	S
Sodium oxybate	Narcolepsy	17-Jul-2002	13-Oct-2005	NA	P,O
Aripiprazole	Schizophrenia	15-Nov-2002	4-Jun-2004	11-Jun-2003	S
Atomoxetine*	ADHD	26-Nov-2002	27-May-2004	9-Nov-2004	S
Eletriptan*	Migraine	26-Dec-2002	12-Feb-2001	25-Aug-2011	S
Ziprasidone	Schizophrenia	5-Feb-2001	NA	18-Mar-2002	S
Galantamine*	Alzheimer's disease	28-Feb-2001	14-Sep-2000	NA	S
Almotriptan*	Migraine	7-May-2001	1-Oct-2000	NA	S
Frovatriptan*	Migraine	8-Nov-2001	7-Oct-2002	NA	S
Cevimeline	Sjogren's Syndrome	11-Jan-2000	NA	NA	S
Oxcarbazepine*	Epilepsy	14-Jan-2000	7-Jan-2000	30-Oct-2001	S
Zonisamide	Epilepsy	27-Mar-2000	10-Mar-2005	21-Dec-2005	S
Articaine/Epinephrine	Anesthesia for dentistry	3-Apr-2000	A	A	S
Rivastigmine	Alzheimer's disease	21-Apr-2000	12-May-1998	28-Jan-2008	S
Zaleplon	Insomnia	13-Aug-1999	12-Mar-1999	17-Jan-2002	S
Entacapone	Parkinson's disease	19-Oct-1999	16-Sep-1998	30-Dec-2004	S
Levetiracetam	Epilepsy	30-Nov-1999	29-Sep-2000	4-Apr-2005	S
Dexmedetomidine	Sedation	17-Dec-1999	16-Sep-2011	29-May-2009	S
Melatonin	Insomnia	NA	29-Jun-2007	NA	
Stiripentol	Epilepsy	NA	4-Jan-2007	NA	
Eslicarbazepine	Epilepsy	NA	21-Apr-2009	7-Mar-2011	
Fampridine	Multiple Sclerosis	NA	20-Jul-2011	NA	
Amifampridine	Lambert-Eaton Myasthenic Syndrome	NA	23-Dec-2009	NA	
Agomelatine	Major depressive disorder	NA	19-Feb-2009	NA	
Retigabine	Epilepsy	NA	28-Mar-2011	NA	
Tafamidis	Amyloidosis	NA	16-Nov-2011	NA	

Tiapride	Schizophrenia	NA	A	23-Jun-2011	
Tofisopam	Anxiety disorder	NA	A	13-Apr-2010	
Zotepine	Schizophrenia	NA	A	15-Apr-2010	
Armodafinil	Narcolepsy	15-Jun-2007	NA	23-Apr-2010	S
Opipramol	Anxiety disorder	NA	NA	13-Nov-2010	
Betahistine	Meniere's disease	NA	A	20-Feb-2009	
Ropivacaine	Local or regional anesthesia	24-Sep-1996	3-Oct-1995	19-Mar-2009	S
Methadone	Opioid dependence	A	A	28-May-2009	
Naratriptan	Migraine	10-Feb-1998	28-Apr-2002	18-Jul-2009	S
Citicoline	Nootropic	NA	A	20-Aug-2004	
Levosulpiride	Schizophrenia	NA	NA	26-Sep-2008	
Glatiramer Acetate	Multiple sclerosis	20-Dec-1996	7-Apr-2003	21-Feb-2007	S,O
Epalrestat	Diabetic neuropathy	NA	NA	25-May-2007	
Edaravone	Acute ischemic stroke	NA	NA	26-Jul-2007	
Etizolam	Anxiety disorder	NA	NA	29-Oct-2007	
Desflurane	Anesthesia	18-Sep-1992	A	22-Feb-2006	S
Amisulpride	Schizophrenia	NA	A	1-Aug-2006	
Pramipexole	Parkinson’s disease	1-Jul-1997	14-Oct-1997	25-Jul-2005	S
Cabergoline*	Parkinson’s disease	23-Dec-1996	14-Feb-1996	7-May-2004	S
Tiagabine	Epilepsy	30-Sep-1997	A	14-May-2004	S
Escitalopram	Major depressive disorder	14-Aug-2002	10-Jun-2002	24-Jan-2003	S
Rizatriptan*	Migraine	29-Jun-1998	1-Jun-1998	27-Feb-2003	S
Vinpocetine	Nootropic	NA	A	13-May-2002	
Modafinil*	Narcolepsy	24-Dec-1998	14-Oct-1997	15-Dec-2003	S,O
Sufentanil	Anesthesia	4-May-1984	A	17-Dec-2003	P
Divalproex	Epilepsy	10-Mar-1983	A	17-Jan-2002	S
Methyl Cobalamin	Peripheral neuropathy	NA	NA	13-Feb-2002	
Quetiapine	Schizophrenia	26-Sep-1997	31-Jul-1997	31-May-2002	S
Fosphenytoin	Epilepsy	5-Aug-1996	A	1-Oct-2002	S
Reboxetine*	Major depressive disorder	NA	10-Apr-1997	31-Dec-2002	
Mirtazapine*	Major depressive disorder	14-Jun-1996	16-Mar-1994	14-Feb-2001	S
Donepezil*	Alzheimer's disease	25-Nov-1996	14-Feb-1997	20-Mar-2001	P
Citalopram*	Major depressive disorder	17-Jul-1998	17-Mar-1995	3-Oct-2001	S
Ropinirole*	Parkinson’s disease	19-Sep-1997	2-Jul-1996	3-Dec-2001	S
Olanzapine	Schizophrenia	30-Sep-1996	27-Sep-1996	27-Jan-2000	S
Fluvoxamine Maleate	Major depressive disorder	5-Dec-1994	A	21-Feb-2000	S
Moclobemide*	Major depressive disorder	NA	19-Jun-1991	28-Jul-2000	
Venlafaxine*	Major depressive disorder	28-Dec-1993	22-Nov-1994	18-Sep-2000	S
Paroxetine*	Major depressive disorder	29-Dec-1992	20-Jun-1991	4-Oct-2000	S
Zolpidem	Insomnia	16-Dec-1992	A	28-May-1999	S
Zuclopenthixol Acetate*	Schizophrenia	NA	16-Mar-1990	29-Jul-1999	
Topiramate*	Epilepsy	24-Dec-1996	18-Jul-1995	23-Aug-1999	S
Sulpiride*	Schizophrenia	NA	6-May-1983	26-Oct-1999	

INN: International Nonproprietary Name, NA: Not Available, A: Available, but approval date is not known, P: Priority review drug, S: Standard review drug, O: Orphan drug, ADHD: Attention-Deficit Hyperactivity Disorder.

*UK approval date

The approval dates and characteristics of new nervous system drugs approved either in the US, EU or India is shown in Table 2. Of the 72 new nervous system drugs that were approved by the FDA, 10 were priority review drugs; 61 were standard review drugs; 9 received orphan drug status and the US review type status was not available for one drug.

DISCUSSION

The percentage of approval of new nervous system drugs was almost similar in the three regions (74.22% for the US, 78.35% for the EU and 77.31% for India). Thus, India is not behind in comparison to the US and EU regions in terms of absolute drug lag. The EU was the first to approve the majority of new nervous system drugs (50%) and the US was the first to approve almost 41% of drugs (Median approval lag for the US and EU: 0 month). But, the considerable delay was observed for India in approval of new nervous system drugs. The median approval lag for India (48.95 months) was more than 4 years longer than that for the US (0 month) and EU (0 month). Therefore, it can be assumed that generally for most of the drugs development process start simultaneously in the US and EU regions. But in comparison with the US and EU, a striking relative drug lag was observed for approval of new nervous system drugs in India.

It is not possible to make an analysis of the possible reasons behind these delays in this study. However, delay in the start of development, delay in the progress of development and delay in review by the regulatory authority could be possible reasons behind these delays in approval of nervous system drugs in India. Besides, delay in review by the regulatory authority, this study suggests that the drug lag may be associated with delays in the initiation of drug development in India. One possible reason for the delays may be that pharmaceutical companies believe that simultaneously conducting registration trials in India and in the US or EU is a risk. As per World Trade Organisation (WTO), from the year 2005, India granted product patent recognition to all new chemical entities (NCEs). Though, many foreign multinational corporations (MNCs) are not taking risk to launch their patented new drugs in India simultaneously with the developed markets. To resolve delays in the initiation of drug development in India, pharmaceutical companies should make an effort to enrol Indian patients in international registration trials. For majority of new drugs, drug development is being performed in the US and the EU concurrently, and the integrated data package may be used for new drug applications (NDAs) in the US and the EU. Thus, it was not surprising that there was a little time gap in new drug approvals between the US and the EU.

Marketing authorisation for Milnacipran, intended for the treatment of fibromyalgia in adults was refused by the EMA, but it is approved in the US and India.[5-7] The FDA declined Pharmacia's license application for Reboxetine in May 2001.[5] In the EU Desvenlafaxine has not been approved for any indication. In 2008, Wyeth withdrew its application for Desvenlafaxine (Ellefore), the product under review for treatment of major depressive disorder.[6] The Committee for Medicinal Products for Human Use (CHMP) of the EMA had some concerns and was of the provisional opinion that Desvenlafaxine (Ellefore) could not have been approved for the treatment of major depressive disorder and overall, the effectiveness of Desvenlafaxine (Ellefore) had not been shown convincingly. In relation to its parent substance, venlafaxine, desvenlafaxine seemed to be less effective with no advantages in terms of safety and tolerability. Apomorphine is now withdrawn from use in the European Union.[6] Eszopiclone is not marketed in the European Union following a 2009 decision by the EMA denying it new active substance status, in which it ruled that eszopiclone was too similar to zopiclone to be considered a new patentable product.[6]

Safety-based withdrawals of drugs or their labels, however, show a beneficial aspect of the drug lag. A typical example is Rofecoxib, which was withdrawn from the market because of its association with cardiovascular problems in September 2004.[10] In the area of psychiatric drugs, the black box warnings of antidepressants for children[11] and of antipsychotics for the elderly with dementia[12] are cases where the drug lag has helped patients to avoid exposure to potentially harmful drugs. The general public as well as most healthcare professionals believe that the drug lag is always bad for patients, but its impact on health outcomes is unknown. A study of the therapeutic significance of the drug lag in the USA in the 1970s[13] showed that only 14% of 198 drugs reviewed offered a potential therapeutic advance, whereas 75% appeared to offer little or no advance.

There is a large gap between India and the west with regard to timing of approval of new nervous system drugs. This may be because the US or Europe based companies were not interested to introduce the new nervous system drugs through their subsidiaries in India due to relaxed patent law in India before 2005. The majority of large multinational pharmaceutical companies have presence in India and they may try to introduce their new products in India, simultaneously with other markets. Now, because of product patent in India, the Indian pharmaceutical companies can't introduce patented drugs developed by the foreign multinational corporations (MNCs). With the introduction of product patents, Indian companies will have to shift the area of focus from process development to developing new drug products.

There is a need to improve the regulatory processes in India to enhance the clinical trial and new drug approvals. The Indian regulatory authority has to initiate some measures to reduce this delay in approval. The Japanese government has initiated various direct and indirect measures to reduce drug lag in Japan.[14] There is an urgent need to increase the human resources and improvement in the regulatory processes in India.[15]

In conclusion, this study confirms that there is still a large gap between India and the West with regard to access to standard nervous system drugs. The drug lag in India may be attributed to a delay in the start of development, a delay in the progress of development, late submission of NDA and a delay in review by the regulatory authority. The impact of the drug lag on health outcomes remains to be established.

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